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SIGNIFICANCE OF HAPLOTYPE B DONORS AND GENE CONTENT MOTIFS IN NONMYELOABLATIVE, HLA-HAPLOIDENTICAL (Haplo) BMT WITH POSTTRANSPLANTATION HIGH-DOSE CYCLOPHOSPHAMIDE (PT/Cy)

Symons, H.J., Munchel, A.T., Rossiter, N.L., Kasamon, Y.L., Jones, R.J., Fuchs, E.J., Leffell, M.S. Johns Hopkins University, Baltimore, MD

Killer immunoglobulin receptors (KIRs) regulate natural killer cell function, and can influence BMT outcome. We studied the relationship of KIR haplotype and gene content motifs in 208 patients who received nonmyeloablative haploBMT and PT/Cy with the goal of identifying a clinically applicable donor selection strategy that could improve the success of this transplant platform. The preparative regimen consisted of fludarabine (30 mg/m^2 IV days -6 to -2), Cy (14.5 mg/kg IV days -6 and -5), total body irradiation (200 cGy day -1), and T-cell replete bone marrow infusion. GVHD prophylaxis consisted of PT/Cy (50 mg/kg IV days 3 and 4), mycophenolate mofetil days 5-35, and tacrolimus days 5-180. All patients (median age 52, range 1-73) had poor-risk hematologic malignancies (65% lymphoid and 35% myeloid). 75% of recipients had Haplotype B donors. Median follow-up was 2.7years (range, 0.5-5years), for those without events. We confirmed that recipients with haplotype B/x donors had an improved overall survival (OS) (median 1081 vs. 608 days, p = 0.06) and progression free survival (PFS) over those with A/A donors (median 363 days vs. 170 days, p = 0.06) (Table 1), as previously reported. Interestingly, a protective effect of donor B/x was observed on OS and PFS for those with lymphoid malignancies (p = 0.01 and p = 0.03, Table 1), but not for those with myeloid malignancies. In order to identify which particular donor B-specific genes improved outcome, centromeric (Cen) and telomeric (Tel) parts of the KIR locus were assigned according to the presence or absence of one or more B haplotype-defining KIR genes. We found a significant benefit on OS and PFS from donors with a Cen A/B genotype as compared with Cen A/A (p = 0.03, p = 0.03) as well as some benefit from the Tel B/B genotype as compared with Tel A/A (p = 0.06, p = 0.09). Donors with KIR B-content scores of ≥2 had a tendency towards an improved OS (p = 0.1) and PFS (p = 0.06) (Table 1). We found no effect of KIR haplotype on relapse or acute GVHD, however there was a tendency towards an improved non-relapse mortality in lymphoid recipients with haplotype B donors (p = 0.1) and in all recipients with Cen A/B donors (p = 0.12). We did not see a significant benefit of inhibitory KIR gene mismatches on outcome. Selection of haplotype B donors, particularly for A/A recipients with lymphoid malignancies, may be warranted after haploBMT with PT/Cy. Further selection of donors with Cen A/B and/or Tel B/B genotypes may also be useful.

Table 1. Effect of KIR Haplotype and Gene Content Motifs on OS and PFS

	N	Median OS (days)	OS p-value	Median PFS (days)	PFS p-value
Donor Haplotype					
Entire Cohort					
B/x	153	1081	0.06	363	0.06
A/A	55	608		170	
Lymphoid					
B/x	36	887	0.01	432	0.03
A/A	97	215		153	
Donor B Content					
Entire Cohort					
>/ = 2	58	1308	0.1	474	0.06
< 2	150	681		202	
Lymphoid					
>/ = 2	38	1308	0.07	469	0.15
< 2	95	441		201	
Donor Cen Genotype					
Entire Cohort					
A/B	95	1308	A/B vs A/A 0.03	432	A/B vs A/A 0.03
B/B	24	586	A/B vs B/B 0.19	333	A/B vs B/B 0.70
A/A	89	580	B/B vs A/A 0.87	198	B/B vs A/A 0.32
Lymphoid					
A/B	62	1308	A/B vs A/A 0.03	441	A/B vs A/A 0.19
B/B	14	477	A/B vs B/B 0.14	218	A/B vs B/B 0.34
A/A	57	268	A/A vs B/B 0.97	201	A/A vs B/B 0.10
Donor Tel Genotype					
Entire Cohort					
B/B	24	undefined	B/B vs A/A 0.06	1147	B/B vs A/A 0.09
A/B	65	814	B/B vs A/B 0.09	246	B/B vs A/B 0.14
A/A	130	681	A/A vs A/B 0.59	213	A/B vs A/A 0.79
Lymphoid					
B/B	9	undefined	B/B vs A/A 0.06	1365	B/B vs A/A 0.08
A/B	42	887	B/B vs A/B 0.09	388	B/B vs A/B 0.20
A/A	82	441	A/A vs A/B 0.25	178.5	A/A vs A/B 0.23

OS = Overall survival; PFS = Progression Free Survival; Cen = Centromeric; Tel = Telomeric.

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BENEFICIAL EFFECT OF HIGH-DOSE IV BUSULFAN (BU) DELIVERED BY PROLONGED CONTINUOUS INFUSION (CI) ON RELAPSE RATE AND OVERALL SURVIVAL (OS) IN MATCHED RELATED AND UNRELATED ALLOGENEIC TRANSPLANT PATIENTS WITH HEMATOLOGIC MALIGNANCIES

Walko, C.[1], Ivanova, A.[2], Whitley, J.[1], Rao, K.[3], Gabriel, D.[1], Serody, J.[1], Comeau, T.[1], Coghill, J.[1], Armistead, P.[1], Sarantopoulos, S.[1], Wood, W.[1], Shea, T.[1] [1] The University of North Carolina at Chapel Hill and Lineberger Comprehensive Cancer Center, Chapel Hill, NC; [2] The University of North Carolina at Chapel Hill and Lineberger Comprehensive Cancer Center, Chapel Hill, NC; [3] The University of North Carolina at Chapel Hill, Chapel Hill, NC

Introduction: Dose escalation of chemotherapy and radiation in allogeneic transplant conditioning regimens has lowered relapse rates but not usually improved overall survival because of higher treatment related mortality. The availability of IV BU has allowed more precise dosing and dose escalation of this drug.

Methods: Test dose (.8 mg/kg) BU was administered one week prior to start of the conditioning regimen and the desired AUC calculated from the clearance. Dose levels were escalated in 20% increments from 4800 to 5760, 6912, 7603 and 8663 uM-min/24 hours from day -7 to -3 over 90 hours with fludarabine, 30 mg/m^2/d on days -7 to -3. All pts received tacrolimus and either alemtuzamab alone, or low dose methotrexate (mtx) +/- ATG for GVH prophylaxis.

Results: 55 high risk pts, age 39 (22-54), 20 MRD, 35 MUD, 29 AML, 7 ALL, 8 MDS, 5 NHL, 6 other, were enrolled on this IRB approved study. 30 pts received alemtuzamab, 19 ATG + mtx and 6 mtx only. Mean achieved AUCs by dose level were 4973 (14 pts), 5638 (7 pts), 7131 (25 pts), 7053 (7 pts), and 8680 (2 pts) uM-min/24 hrs. The MTD was level 3. Grade 4 DLTs were mucositis in 2/2 at level 5 and 1/7 at level 4 and reversible VOD in 1/7 at level 4. Three additional grade 5 treatment-related toxicities were seen at dose level 1 (liver failure), level 2 (mucositis) and level 3 (VOD). The total incidence of grade 4 or 5 VOD was 2/55 or 4%. When divided by AUC into three groups of 19, 19, and 17 pts each, median AUC values were 5106, 6431, and 7693 uMol-min/24 hrs, respectively. Median OS in days were 298, 353, and Not Reached and times to relapse were 191, 353, and 818, for the lowest, middle and highest AUC groups, respectively. Two-year OS and RFS for the lowest, middle and highest groups were .24, .41, and .70 and .20, .35, and .63, respectively. Differences in relapse and OS were significant at the .053 and .063 levels, respectively. Relapse related death was much higher in the lowest AUC group (9/19 vs 1/17, p = .013), but there was no difference in non-relapse deaths between the groups; 6/19, 7/19, and 4/17, p = .663. In multivariable analysis, higher AUC dose, use of ATG rather than alemtuzamab and having a MUD demonstrated a trend toward improved outcomes with AUC being the strongest predictor.

Conclusion: High AUC levels of busulfan can be safely achieved with CI leading to improved overall survival and decreased relapse rates in patients undergoing matched related or unrelated allogeneic transplantation.